FDA Risk Management Draft Guidances

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Risk Assessment Guidance

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc

Good Reporting Practice

- Spontaneous Reports
- Complete and accurate reports
- Focus efforts based on:
  - New
  - Seriousness
  - Report origin
  - other

Elements of Report

- Description of AE, time to onset
- How diagnosis made
- Drugs & Biologics taken, dose, frequency
- Patient characteristics
- Clinical course and outcome
- Lab and other test results
- Rechallenge/Dechallenge

Categorization of Causality for an Individual Case

- No specific categorization recommended
- WHO's mentioned

  -certain

  -probably/likely

  -possible

  -unlikely

  -conditional/unclassified

  -unassessable/unclassifiable.

Medication Error Report

- Products involved
- Sequence of events leading to error
- Work environment
- Personnel involved
- Contributing factors

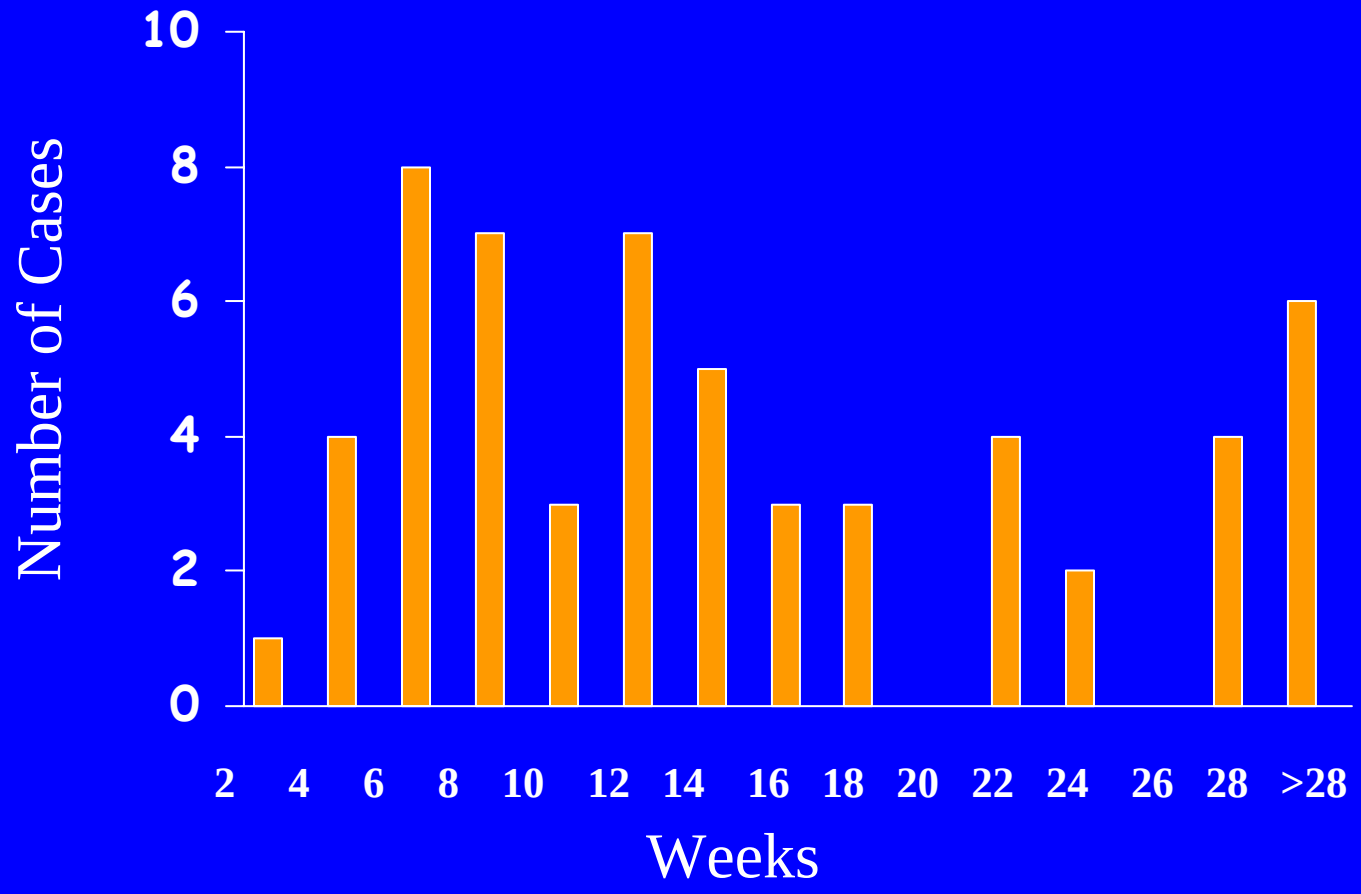
Medication Errors

- Root cause analysis
- Follow-up with reporter
- Systems approach
- Identify failure points/solutions

Case Series Descriptive Analysis

- Demographics of patients
- Clinical and lab findings
- Time to onset
- Dose and duration of therapy, route of administration
- Concomitant medications
- Comorbid conditions
- Product lot

Time From Initiation of Infliximab Therapy to Diagnosis of Tuberculosis



N Eng J Med. 2001;345:1098-104.

VACCINE ADVERSE EVENT REPORTING SYSTEM

VAERS

24 Hour Toll-free information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

For CDC/FDA Use Only

VAERS Number _____

Date Received _____

Patient Name:

_____
Last First M.I.

Address

_____

_____

_____

_____
City State Zip

Telephone no. (_____)_____

Vaccine administered by (Name):

_____

Responsible Physician _____

Facility Name/Address

_____

_____

_____

_____
City State Zip

Telephone no. (_____)_____

Form completed by (Name):

_____

Relation to Patient ☐ Vaccine Provider ☐ Manufacturer ☐ Patient/Parent ☐ Other

Address *(if different from patient or provider)*

_____

_____

_____

_____
City State Zip

Telephone no. (_____)_____

1. State	2. County where administered	3. Date of birth mm / dd / yy	4. Patient age	5. Sex ☐ M ☐ F	6. Date form completed mm / dd / yy

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:

- ☐ Patient died (date ___/___/___ mm dd yy)
- ☐ Life threatening illness
- ☐ Required emergency room/doctor visit
- ☐ Required hospitalization (_____days)
- ☐ Resulted in prolongation of hospitalization
- ☐ Resulted in permanent disability
- ☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

12. Relevant diagnostic tests/laboratory data

10. Date of vaccination ___/___/___ mm dd yy

Time _____ AM PM

11. Adverse event onset ___/___/___ mm dd yy

Time _____ AM PM

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other /unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under

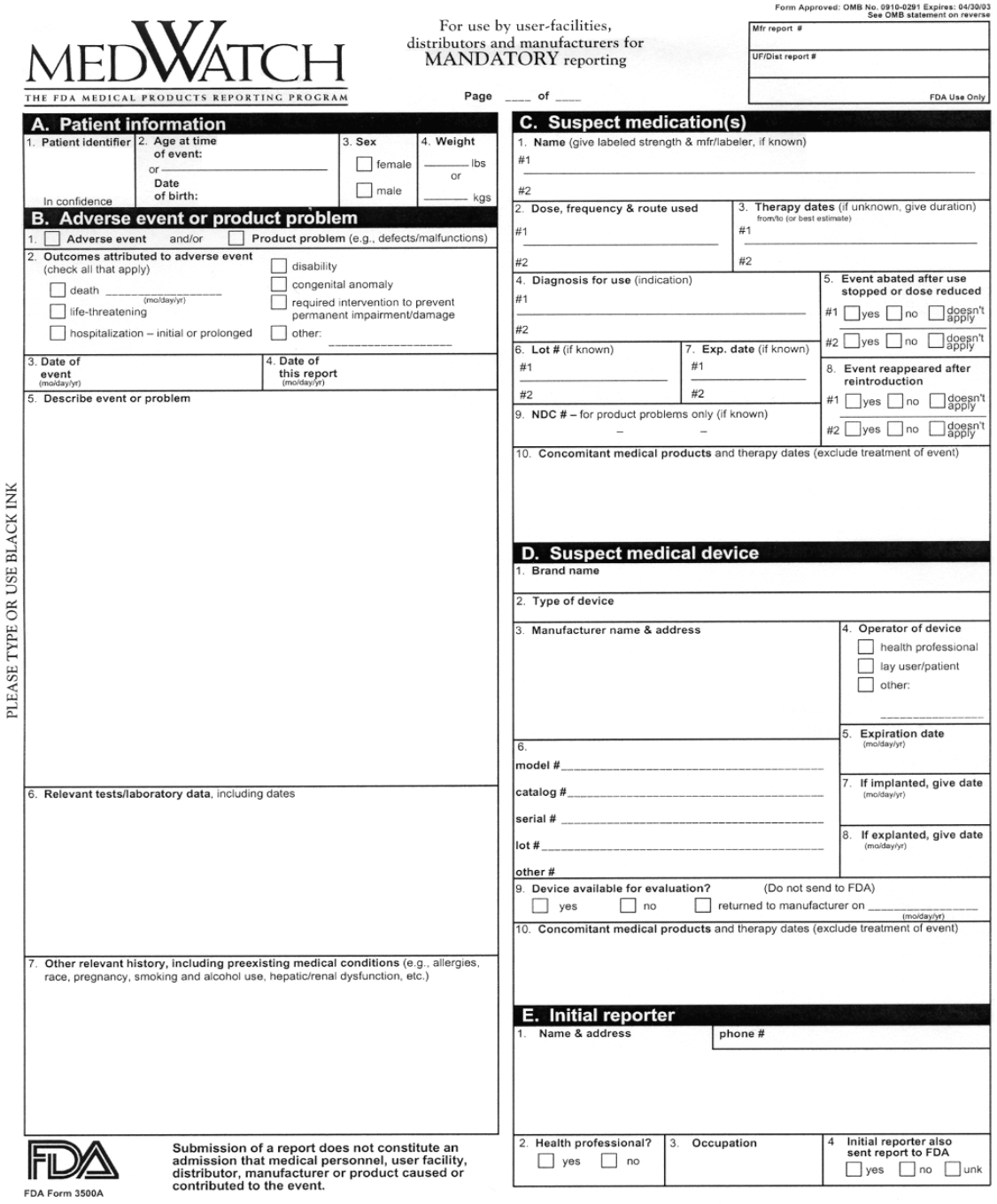
22. Birth weight _____ lb. _____ oz.

23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

Only for reports submitted by manufacturer/immunization project

MedWatch 3500A Mandatory Reporting Form



MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

Page ____ of ____

Mfr report #
UF/Dist report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: female / male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply): death (mo/day/yr); life-threatening; hospitalization – initial or prolonged; disability; congenital anomaly; required intervention to prevent permanent impairment/damage; other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 #2
2. Dose, frequency & route used #1 #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply; #2 yes no doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 yes no doesn't apply; #2 yes no doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device: health professional; lay user/patient; other:
5. Expiration date (mo/day/yr)
6. model # catalog # serial # lot # other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) yes no returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
phone #
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Reporting rates & Incidence rates

- Are not the same!
- Difficult to obtain numerators and denominators
- Biases in reporting rates
- Issues with subpopulations
- But…useful in signal evaluation

Assessing Causality for a Case Series

- Adverse event onset after product administration?
- Time to onset
- Rechallenge/dechallenge
- Consistency with biological action of product
- Consistency with class effects
- Data from other studies
- Confounding/bias present?

"Data Mining"

- Applied to large adverse event databases
- Essentially ratios of proportions
- Observed:expected
- Various, similar methods
- Hypothesis generating
- Additional information needed

Safety Signals for Further Investigation

- Unlabelled AEs, especially serious
- Increased severity of labeled AE
- Serious AEs that are otherwise rare
- Interactions
- New at-risk population
- Medication errors
- AEs Related to off-label use
- Related to RiskMAP

Pharmacoepidemiologic Safety Studies

When an important adverse event-product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic safety studies.

Pharmacoepidemiologic Safety Studies: Choosing a Database

- Demographics, geography
- Patient turnover
- Medications of interest
- Population size
- Outcomes of interest
  - Availability
  - Coding
- Access to Medical Records
- Study should have protocol!

Registries

- Can study outcomes or exposures
- For information:
  - Not otherwise available
  - From multiple sources
- Should have protocol
- Should specify objectives

Surveys

- Instruments should be validated
- Should have protocol
- Can assess:
  - an AE,
  - RiskMAP
  - medication errors
  - off-label use

FDA assessment of safety risk

- Strength of association
- Temporal association
- Consistency of findings
- Dose-response
- Biologic plausibility
- Seriousness of event
- Preventability
- Other factors

Pharmacovigilance Plan

…pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting…designed to enhance and expedite the sponsor's acquisition of safety information. The development of pharmacovigilance plans may be useful at the time of product launch or when a safety signal is identified during product marketing.

Pharmaocovigilance plans may be appropriate for products for which:

(1) safety signals have been identified pre- or post-approval, (2) at-risk populations have not been adequately studied, or (3) other significant safety concerns exist

Pharmacovigilance Plans Could Include

- Expedited submission of adverse events
- More frequent submission of AE summaries
- Active surveillance
- Pharmacoepidemiologic studies
- Registries or surveys
- Clinical trials

ICH E2E "Pharmacovigilance Planning"

- Industry & regulators have identified need for better & earlier plan of pharmacovigilance activities before a license is granted.
- Knowledge can change over time
- Information from Pharmacovigilance fed back to medication users can improve benefit-risk balance

ICH E2E "Pharmacovigilance Planning"

- Main focus is on pharmacovigilance plan submitted at the time of license application
- New chemical entities, biotech products, but also significant changes in established products, such as new populations, new indications

Principles

- Planning of Pharmacovigilance throughout product life-cycle
- Science-based approach to risk documentation
- Regulator-industry collaboration
- Applicability across 3 regions

ICH E2E Document on Pharmacovigilance Planning: 3 Main Components

- Safety Specification
- Pharmacovigilance Plan
- Annex -- PV Methods

ICH Safety Specification

- Can be stand-alone but elements can also be incorporated into the Common Technical Document for a new or modified product

Safety Specification: Non-clinical

Toxicity

General pharmacology

Effect of hepatic and renal function

Drug interaction

Other

Safety Specification: Clinical

- Limitations of the human safety database
  - Size of study population
  - Exclusions/inclusions
- Worldwide…
  - Exposure
  - Safety issues?
  - Regulatory actions?

Safety Specification: Clinical

- Populations not studied pre-approval
  - Children
  - Elderly
  - Pregnant/lactating
  - Hepatic/renal disorders
  - Genetic polymorphisms
  - Racial/Ethnic

Safety Specification: More detailed information on the most important ADRs

- Evidence bearing on causality
- Severity
- Seriousness
- Frequency and at-risk groups

Safety Specification: Other

- Food-drug and drug-drug interactions
- Potential risks that need further evaluation
- Epidemiology of the indication
- Epi of important adverse events
- Pharmacologic class effects

Safety Specification: Summary

- Important identified risks
- Important potential risks
- Important missing information

ICH Pharmacovigilance Plan

- Summary of ongoing safety issues, especially if Pharmacovigilance Plan is separate document

Pharmacovigilance Plan: Routine Practices

- ADR reports are accessible
- PSURs & Expedited Reports
- Continuous safety profile monitoring
- Signal detection
- Issue evaluation
- Updating of labeling
- Liaison with regulatory authorities

Pharmacovigilance Plan: Safety Action Plan

- Risk issue or important missing information
- Objective of proposed action
- Action proposed
- Rationale for proposed action
- Oversight within the company
- Milestones

Pharmacovigilance Methods

- Protocol, with at a minimum
  - Aims/objectives, methods, analytic plan
- Study report(s)
  - Objectives, methods, results, PI's interpretation of findings
- ISPE Guidelines

Annex defines…

- Passive surveillance: spontaneous reports, "datamining", case series
- Intensified reporting
- Active Surveillance
- Sentinel sites
- Drug-event monitoring
- Registries
- Comparative observational studies: cross-sectional survey, case-control study, cohort study
- Targeted clinical investigations
- Descriptive studies: natural history of disease, drug utilization